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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,867	02/27/2004	George A. Heavner	CEN0320CIP1	1167

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EXAMINER	
SPECTOR, LORRAINE	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 11/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,867	HEAVNER ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Subject to the amendment filed 8/29/2006, claims 4 and 13 are pending and under consideration. The restriction requirement is moot in view of the cancellation of all non-elected claims.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is indefinite for claiming "at least one" mutant; it cannot be determined how many mutants are being claimed, and whether all of them must meet the remaining limitations of the claim or not. The claim is further indefinite as it is not clear whether applicants intend to claim an IL-13 mutein having a Gln or Asn at position 130 *and* one of more of the other mutations listed, or whether the other mutations are referring to a different mutant IL-13, i.e. a mixed composition of different muteins. Finally, the claim is indefinite as Phe103 is the wild-type residue, and is not a substitution.

Claim 13 is rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is specific muteins of human IL-13. While muteins of IL-13 are known in the art, the specific muteins claimed are not. The claimed muteins have been generated using computer modeling techniques. *None* of the claimed muteins was actually produced, nor tested for activity. While the claims do not require that the claimed muteins be biologically active, the specification has not taught how to use those that are not. Generally, in the art, computer modeling is subsequently verified by actually making the predicted proteins; it is not accepted in the art that modeling has progressed to a point that it can accurately predict active species. In the instant case, the art teachings would lead the person of ordinary skill in the art *not* to expect the claimed muteins to be active, specifically Oshima et al. (JBC 275:14375-14380, 2000), at figure 1A, show an alignment of mouse, rat, human, and bovine (bos Taurus) IL-13 sequences. The alignment there would lead the person of ordinary skill in the art to the following conclusions:

Substitution of Gln or Asn at position 130: The residue at the position corresponding to residue 130 of SEQ ID NO: 1 of this application is conserved across all four species. The naturally occurring residue is Lysine, which is a basic amino acid residue. Both Gln and Asn are uncharged amino acids, thus the substitution is a "non-conservative" substitution. The person of ordinary skill in the art would not expect that an uncharged amino acid

such as Gln or Asn could be substituted at this site with a reasonable expectation of success at retaining protein function, as such is not a conservative substitution, and the conservation of the residue across all four species indicates evolutionary pressure to maintain the Lys residue.

Substitution of Val or Ile at position 48: The residue at the position corresponding to residue 48 of SEQ ID NO: 1 of this application (marked by hand on the figure) is conserved across all four species. The naturally occurring residue is Glutamic Acid, which is an acidic residue. The person of ordinary skill in the art would not expect such a conserved position to be tolerable to substitution, much less a non-conservative substitution of Val or Ile, which are both uncharged amino acids, for an acidic amino acid.

Substitution of Glu or Gln at position 90: Again, this residue is a conserved cysteine, across all five species shown by Oshima et al. Oshima et al. comment in the caption to the figure that the four cysteine residues are "completely conserved between the four species". The person of ordinary skill in the art would be aware that cysteine residues are important to the secondary structure of proteins, as they form disulphide bonds. The person of ordinary skill in the art would not expect that a conserved cysteine residue could be substituted with a reasonable expectation of success at retaining protein function.

Substitution of Leu or Ile at position 95: The naturally occurring residues at this position are Arginine and Lysine, both basic amino acids. The person of ordinary skill in the art would not expect that an uncharged amino acid such as Leu or Ile could be substituted at this site with a reasonable expectation of success at retaining protein function, as such is not a conservative substitution.

Substitution of Leu or Ile at position 96: The residue at the position corresponding to residue 96 of SEQ ID NO: 1 of this application is conserved across all four species. The naturally occurring residue is Threonine, which is an uncharged residue. Although both Leu and Ile are also uncharged amino acids, the person of ordinary skill in the art would not consider it predictable that such a conserved position (indicating evolutionary

pressure to maintain the threonine residue at that position) would be tolerable to substitution with a reasonable expectation of success at retaining protein function.
Substitution of Leu or Ile at position 99: The naturally occurring residues at this position are Ile (mouse and rat) or Met (human and bovine). Accordingly, there is a reasonable expectation of success at making this substitution.
Substitution of Tyr at position 103: The naturally occurring residues at this position are Leu (mouse, rat, bovine) and Phe (human), both uncharged residues. Tyrosine is also an uncharged residue. Accordingly, there is a reasonable expectation of success at making this substitution.

Thus, of the seven substitution sites, only two would reasonably be expected to maintain protein function, and the person of ordinary skill in the art would still not predict such solely based upon sequence information, but would make and test the substitutions. The Examiner notes that even when a single substitution is shown to be functional, the effect of combining different substitutions in a single protein is not predictable. There are 2x3x3x3x3x3x2, or 972 species or protein encompassed by the claims. There are no working examples in which any muteins were actually made or tested for activity, and the prior art notably does *not* contain reports of substitutions at any of the claimed sites, although numerous IL-13 muteins *are* known in the art, for example see Oshima, who made a mutation at position 112 (R112D) and showed the mutation to produce a high affinity IL-13 agonist, U.S. Patent No. 6,576,232 (Debinski et al), which made IL-13 muteins based upon structural predictions *and tested them for activity* (nnote that Debinski's numbering is different than that of SEQ ID NO: 1), and Oshima-2 (Oshima et al., JBC 276:15185-91, 2001) who made IL-13 antagonists by use of structural models that made use of similarity to IL-4, coupled with biological testing.

With further respect to biological activity, it is noted that IL-13 is a complex cytokine: it shares a receptor with IL-4, as well as having a separate receptor that is not shared. Accordingly, in addition to considering the predictability of retention of function, the situation is further complicated by there being multiple functions to consider. Hence, it would require undue experimentation to make and use the invention.

Conclusion

The claims are free of the prior art. The Examiner is unable to identify any prior art in which position 130 of human IL-13 has been substituted by another amino acid.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lorraine Spector, Ph.D.
Primary Examiner